4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2018-N-3262]

Determination That CEFZIL (Cefprozil) Tablets, 250 Milligrams and 500 Milligrams, and for Oral Suspension, 125 Milligrams/5 Milliliters and 250 Milligrams/5 Milliliters, Were Not Withdrawn From Sale for Reasons of Safety or Effectiveness

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA or Agency) has determined that CEFZIL (cefprozil) tablets, 250 milligrams (mg) and 500 mg and CEFZIL (cefprozil) for oral suspension, 125 mg/5 milliliters (mL) and 250 mg/5 mL were not withdrawn from sale for reasons of safety or effectiveness. This determination will allow FDA to continue to approve abbreviated new drug applications (ANDAs) that refer to these drugs as long as they meet relevant legal and regulatory requirements.

FOR FURTHER INFORMATION CONTACT: Diana J. Pomeranz, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6288, Silver Spring, MD 20993-0002, 240-402-4654.

SUPPLEMENTARY INFORMATION: In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417) (the 1984 amendments), which authorized the approval of duplicate versions of drug products under an ANDA procedure. ANDA applicants must, with certain exceptions, show that the drug for which they are seeking approval contains the same active ingredient in the same strength and dosage form as the "listed

drug," which is a version of the drug that was previously approved. ANDA applicants do not have to repeat the extensive clinical testing otherwise necessary to gain approval of a new drug application (NDA).

The 1984 amendments include what is now section 505(j)(7) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)(7)), which requires FDA to publish a list of all approved drugs. FDA publishes this list as part of the "Approved Drug Products With Therapeutic Equivalence Evaluations," which is known generally as the "Orange Book." Under FDA regulations, drugs are removed from the list if the Agency withdraws or suspends approval of the drug's NDA or ANDA for reasons of safety or effectiveness or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (21 CFR 314.162).

A person may petition the Agency to determine, or the Agency may determine on its own initiative, whether a listed drug was withdrawn from sale for reasons of safety or effectiveness. This determination may be made at any time after the drug has been withdrawn from sale, but must be made prior to approving an ANDA that refers to the listed drug (§ 314.161 (21 CFR 314.161)). FDA may not approve an ANDA that does not refer to a listed drug.

Under § 314.161(a)(2), the Agency must also determine whether a listed drug was withdrawn from sale for reasons of safety or effectiveness if ANDAs that referred to the listed drug have already been approved prior to its market withdrawal. If the Agency determines that a listed drug was withdrawn from sale for reasons of safety or effectiveness, and there are approved ANDAs that reference that listed drug, FDA will initiate a proceeding to determine whether the suspension of the ANDAs is also required (21 CFR 314.153(b)).

CEFZIL (cefprozil) tablets, 250 mg and 500 mg, are the subject of NDA 050664 held by Corden Pharma Latina S.p.A., and initially approved on December 23, 1991. CEFZIL

(cefprozil) for oral suspension, 125 mg/5 mL and 250 mg/5 mL, is the subject of NDA 050665 held by Corden Pharma Latina S.p.A., and initially approved on December 23, 1991. CEFZIL is indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

- Upper respiratory tract: Pharyngitis/tonsillitis caused by *Streptococcus pyogenes*; otitis media caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* (including β-lactamase-producing strains), and *Moraxella (Branhamella) catarrhalis* (including β-lactamase-producing strains); and acute sinusitis caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* (including β-lactamase-producing strains), and *Moraxella (Branhamella) catarrhalis* (including β-lactamase-producing strains);
- Lower respiratory tract: Acute bacterial exacerbation of chronic bronchitis caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* (including β-lactamase-producing strains), and *Moraxella (Branhamella) catarrhalis* (including β-lactamase-producing strains); and
- Skin and skin structure: Uncomplicated skin and skin-structure infections caused by *Staphylococcus aureus* (including penicillinase-producing strains) and *Streptococcus pyogenes*. Abscesses usually require surgical drainage.

In a letter dated September 7, 2010, Bristol-Myers Squibb[1] notified FDA that CEFZIL (cefprozil) tablets, 250 mg and 500 mg and CEFZIL (cefprozil) for oral suspension, 125 mg/5 mL and 250 mg/5 mL, were discontinued from sale, and FDA moved the drug products to the "Discontinued Drug Product List" section of the Orange Book. Later, Corden Pharma Latina

[1] On May 26, 2011, Bristol-Myers Squibb transferred ownership of NDA 050664 and NDA 050665 to Corden Pharma Latina S.p.A.

S.p.A. notified the Agency in writing that these drug products were no longer marketed and requested that the approval of the applications be withdrawn. In the *Federal Register* of June 21, 2017 (82 FR 28322 at 28326), the Agency issued a notice withdrawing approval of the applications, effective July 21, 2017.

After reviewing Agency records and based on the information we have at this time, FDA has determined under § 314.161 that CEFZIL (cefprozil) tablets, 250 mg and 500 mg, and CEFZIL (cefprozil) for oral suspension, 125 mg/5 mL and 250 mg/5 mL, were not withdrawn from sale for reasons of safety or effectiveness.

We note that CEFZIL (cefprozil) tablets, 250 mg and 500 mg, and CEFZIL (cefprozil) for oral suspension, 125 mg/5 mL and 250 mg/5 mL, previously were approved with an indication for secondary bacterial infection of acute bronchitis (SBIAB). On October 3, 2016, FDA sent Corden Pharma Latina S.p.A. a Prior Approval Supplement Request letter seeking removal of the SBIAB indication from the labeling of these drug products. In response, on October 28, 2016, Corden Pharma Latina S.p.A. submitted supplements proposing to remove the indication. On November 22, 2016, FDA approved these supplements and the indication was removed. The ANDA applicants referencing these NDAs subsequently followed suit and submitted supplements proposing to remove the SBIAB indication from their labeling. The Agency approved these supplements.

Further, based on a review of relevant information, FDA concluded that the SBIAB indication is not appropriate because most cases of SBIAB are considered to be viral or non-infectious. As an antibacterial drug, CEFZIL (cefprozil) is not considered to be effective to treat SBIAB. Such use of CEFZIL (cefprozil) would likely result in inappropriate antibacterial drug use. Accordingly, the risk benefit balance for the treatment of SBIAB with CEFZIL (cefprozil)

is unfavorable and does not support approval of these products (or ANDAs referencing them) for this indication.

The Agency will continue to list CEFZIL (cefprozil) tablets, 250 mg and 500 mg, and CEFZIL (cefprozil) for oral suspension, 125 mg/5 mL and 250 mg/5 mL, in the "Discontinued Drug Product List" section of the Orange Book. FDA will continue to accept and, where appropriate, approve ANDAs that refer to these drug products, but does not intend to do so if they propose to include the SBIAB indication (see, e.g., section 505(j)(2)(A)(v) and (j)(4)G) of the FD&C Act and 21 CFR 314.94(a)(8)(iv) and 314.127(a)(7)). If FDA determines that labeling for this drug product should be revised, the Agency will advise ANDA applicants to submit such labeling.

Dated: September 4, 2018.

Leslie Kux,

Associate Commissioner for Policy.

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